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Highlights from the III International Symposium of Thrombosis and Anticoagulation (ISTA), October 14–16, 2010, São Paulo, Brazil

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Abstract To discuss and share knowledge around advances in the care of patients with thrombotic disorders, the Third International Symposium of Thrombosis and Anticoagulation was held in São Paulo, Brazil, from October 14–16, 2010. This scientific program was developed by clinicians for clinicians, and was promoted by four major clinical research institutes: the Brazilian Clinical Research Institute, the Duke Clinical Research Institute of the Duke University School of Medicine, the Canadian VIGOUR Centre, and the Uppsala Clinical Research Center. Comprising 3 days of academic presentations and open discussion, the symposium had as its primary goal to educate, motivate, and inspire internists, cardiologists,

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hematologists, and other physicians by convening national and international visionaries, thought-leaders, and dedicated clinician-scientists. This paper summarizes the symposium proceedings.

Keywords Thrombosis · Antithrombotic therapy · Guidelines · Clinical research

Introduction

Importance of thrombosis

Venous and arterial thrombosis remains the most frequent cause of death in western countries. Cardiovascular disease, including heart attack and stroke, accounts for more than 50% of deaths (http://www.cdc.gov/nchs/fastats/deaths.htm). Additionally, the presence of thromboembolism is an adverse prognostic indicator in patients with cancer, which is the second most common cause of death. As a result, there is great interest in the development of novel anticoagulant agents designed to reduce the risk of first or recurrent thrombotic event while minimizing the risk of bleeding. Arterial thrombosis is generally due to platelet activation occurring at sites of vascular injury in high-flow and high-sheer vessels. Generally, antiplatelet agents are preferred for primary or secondary prevention of arterial thrombosis because they inhibit platelet activation induced by platelet binding at sites of vascular injury and mediated by von Willebrand factor. Recent interest has focused on the development of new and more potent antiplatelet agents with special characteristics including rapid on- and off-set of action, shorter half-lives, and more potent inhibition of specific self-surface receptors including the thrombin receptor.

Venous thrombosis is generally thought to be due to activation of soluble coagulation proteins in low-flow areas of the venous system. There are some parallels in the left atrium of patients with atrial fibrillation (AF), suggesting that treatments that are effective for prevention of venous thrombosis will also be effective for prevention of systemic embolization in patients with AF. Traditional agents for prevention and treatment of venous thrombosis include heparins, low-molecular-weight heparins (LMWH), pentasaccharides, and a variety of parenteral anticoagulants used infrequently in specific circumstances such as patients with heparin-induced thrombocytopenia. Long-term therapy has traditionally been provided by warfarin administered to achieve an international normalized ratio (INR) of 2.0–3.0. The limitations of warfarin—including drug and food interactions, variability within and between patients in dosing requirements, a narrow therapeutic window, and the need for frequent INR monitoring—have led to the development of novel agents that lack some or all of these characteristics. Dabigatran and rivaroxaban are two agents that have been approved for several indications. Dabigatran recently was approved in Canada and the United States for prevention of systemic embolization in patients with AF. These agents, if proven safe in phase IV studies, offer significant advantages over warfarin for prevention of systemic embolization. They are also the subject of studies for secondary prevention of venous thrombosis. In this setting, efficacy of both agents is comparable to warfarin.

Intensification of antithrombotic therapy has a cost. There is clear evidence that bleeding rates increase as patients are treated with more aggressive antithrombotic regimens. Thus, when compared with warfarin alone, bleeding risks increase in patients treated with aspirin and warfarin, and further increase in patients treated with so-called "triple therapy." Risks of bleeding will undoubtedly be even higher in patients who are treated with "quadruple therapy," as novel antiplatelet and antithrombotic agents are brought to market.

There is also evidence that a therapeutic effect can be achieved at lower doses of antithrombotic medications than are currently employed for many indications. Thus, prophylactic doses of pentasaccharide are as effective as therapeutic doses of enoxaparin for prevention of thrombotic and other vascular complications in patients with unstable coronary syndromes. At prophylactic doses, fondaparinux produces less bleeding than enoxaparin, suggesting it may be a preferred agent for treatment in this setting. The pentasaccharide study highlights current thoughts suggesting that "de-intensification" should be considered in selected patients because currently available antithrombotics may maintain their "therapeutic effect" at levels that are associated with a lower rate of "toxicity," predominantly bleeding.

In summary, cardiovascular disease remains a leading cause of death. Significant resources have been invested in the design and evaluation of novel antithrombotic agents, which are now being evaluated for prevention of both first and recurrent thrombotic events in high-risk patients. Demonstration that intensification of anticoagulation is associated with enhanced bleeding risk has led to studies that attempt to de-intensify antithrombotic therapy. Novel agents offer the hope of simplicity of treatment with reduced toxicity; however, their safety must be proven in large patient groups.

ISTA

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14–16, 2010. This scientific program was developed by clinicians for clinicians, and was promoted by four major clinical research institutes: the Brazilian Clinical Research Institute (BCRI), the Duke Clinical Research Institute (DCRI) of the Duke University School of Medicine, the Canadian VIGOUR Centre (CVC), and the Uppsala Clinical Research Center (UCR). It was also supported by the Brazilian Societies of Internal Medicine, Cardiology, Intervention Cardiology, Heart Failure, Nephrology, Intensive Care Medicine, Hematology, Oncology, and Vascular Surgery, by the Latin American Group of Thrombosis and Hemostasis, and by the Anticoagulation Forum from the United States. The chairmen of the meeting were Dr. Renato D. Lopes and Dr. Richard C. Becker, both from Duke University School of Medicine and the Duke Clinical Research Institute, and Dr. David Garcia from the University of New Mexico.

Comprising 3 days of academic presentations and open discussion, the symposium had as its primary goal to educate, motivate, and inspire internists, cardiologists, hematologists, and health care providers by convening national and international visionaries, thought-leaders, and dedicated clinician-scientists to review the scientific evidence in the area of thrombosis. The following is a summary of the symposium proceedings.

Platelet biology

Platelet biology and an advanced understanding of fundamental concepts governing the behavior of platelets, both in terms of pathologic thrombotic events and the support of normal hemostasis, comprise a vital part of identifying targets for drug development and achieving optimal patient care. There are four constructs or functional themes of importance: platelet aggregation, platelet support of coagulation, platelet support of vascular integrity, and platelet support of vascular repair.

The initiation of coagulation is characterized by the assembly of coagulation proteins on tissue factor-bearing cells. This is followed by thrombin generation and, if of sufficient quantity to cause platelet activation, platelet aggregation, assembly of coagulation proteins, and a "burst" of thrombin generation with subsequent clot propagation.

Platelet activation and aggregation occurring at a site of vessel wall injury is characterized by three distinct populations of platelets. The first population is characterized by expression of ligand receptors, which in turn facilitate platelet aggregation. The second is characterized by the expression of phosphatidylserine with support coagulation protein assembly and thrombin generation. The third consists of a population of platelets with predominantly paracrine effects that are required for the important stage of vessel wall healing. This latter population of platelets has been underappreciated in considering the potential effects of long-term, robust platelet inhibition with pharmacological therapy.

Several recent observations shed new light on the important interface between platelets and coagulation protein activation within the developing thrombus. Specifically, the release of platelet polyphosphates has been shown to activate factors XI and XII, facilitating thrombin generation. More recent information also highlights the role of polyphosphates, factor XI, and factor XII as triggers of thrombosis that are not required for normal hemostasis. These observations will likely prompt increasing interest in new targets with the theoretical potential to uncouple thrombosis and hemostasis.

The importance of platelets in both a reparative capacity and as facilitators of inflammation highlights their pleotropic capabilities. Despite being anuclear cells, megakaryocytes within the bone marrow respond to a variety of signals, potentially being reprogrammed in the presence of specific conditions. In addition, the recognition that activated human platelets splice pre-mRNA into mature transcripts supports a highly dynamic capability. Whether platelet antagonists can influence either programming at the level of the megakaryocyte or peripheral circulation splicing of pre-mRNA will require further investigation. It is becoming increasingly clear that platelets no longer can be viewed as passive bystanders to vascular events and systemic conditions.

Measures of platelet function

For the last several decades, measurement of platelet function has been used primarily for diagnosis of intrinsic deficiencies of platelet hemostatic capacity. However, more recent work has focused on platelet function testing as a pharmacodynamic measure of response to platelet-directed therapy. In the treatment of atherothrombosis, inhibition of platelet activation and aggregation plays a central role in attenuating thrombus formation and propagation. Such antagonism of the atherothrombotic process is vital for secondary prevention in patients with acute coronary syndromes (ACS) and after percutaneous coronary intervention (PCI).

Two antiplatelet medications used commonly in these populations are aspirin and clopidogrel. Platelet function testing has documented substantial variability in the pharmacodynamic response to both medications; however, the prevalence and clinical impact of this variability remain largely unknown.

Several methods for assessing platelet responsiveness to clopidogrel or aspirin are available. Light-transmission aggregometry (LTA) is the historical "gold standard" for evaluation of the pharmacodynamic response to platelet-directed medications. The major disadvantages are: (1) increased processing time per sample because of the need to generate platelet rich plasma, and (2) increased inter-operator variability. The vasodilator-activated phosphoprotein (VASP) test measures the intracellular platelet response to medications inhibiting the platelet $P2Y_{12}$ receptor. Like LTA, it is a time-consuming, laboratory-based test that is technically demanding.

Newer point-of-care whole blood aggregation tests are now available. Of these, the VerifyNow® (Accumetric, Inc., San, Diego, CA) and Multiplate® (Verum Diagnostica, Munich, Germany) tests have undergone extensive clinical validation. In the Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel Pretreated Patients Undergoing Elective PCI (POPULAR) study comparing the predictive value of different platelet function tests for thrombotic and bleeding outcomes following elective PCI, the VerifyNow test demonstrated a c-statistic comparable to LTA in its ability to discriminate future thrombotic outcomes. Similarly, the Multiplate test performed well in a large German multicenter study investigating the relationship between its adenosine diphosphate (ADP) test and thrombotic outcomes after PCI.

However, the ability of existing platelet function tests to predict bleeding outcomes is more limited. To date, the association between platelet function measurements and future bleeding outcomes has been equivocal—this remains a key limitation of platelet function testing. Another key limitation of currently available platelet function tests is their inability to reliably report on the composite effect of multiple antiplatelet agents acting via different pathways. A further unresolved question is the ability of a platelet function testing-guided strategy to improve clinical outcomes. Although the recently completed Gauging Responsiveness with a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial did not demonstrate an improvement in clinical outcomes with double-dose clopidogrel in patients with clopidogrel hypo-responsiveness identified using the VerifyNow system, other ongoing trials employing more potent $P2Y_{12}$ inhibitors will provide greater clarity on the clinical utility of platelet function testing.

Proton-pump inhibitor (PPI)–clopidogrel interactions: reality or myth?

In patients with ACS, current clinical practice guidelines recommend the use of dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibition. Aspirin, particularly at higher doses, leads not only to platelet inhibition by the effect on thromboxane A2 but also to effects on the gastric mucosa through the inhibition of prostacyclin. This results in an increased risk of peptic ulcer and gastric bleeding. Addition of clopidogrel to aspirin further increases the risk of adverse gastric bleeding events. To reduce this risk, treatment with proton-pump inhibitors (PPI) is routinely used in patients with previous peptic ulcer and often in patients with risk factors for gastric bleeding such as acute care. In fact, both clopidogrel and PPIs are among the most frequently prescribed pharmacological agents worldwide.

The most important mechanism for a poor response to clopidogrel is variable generation of the active metabolite. Approximately 85% of a clopidogrel dose is hydrolysed by esterases to an inactive metabolite. The remaining clopidogrel is available to be converted to the active metabolite in a process requiring two sequential cytochrome P450 (CYP)-dependent steps with CYP2C19 in both steps. A genetically determined reduced function allele of CYP2C19 slows clopidogrel metabolism, which leads to lower levels of the clopidogrel active metabolite and a lower pharmacodynamic platelet inhibitory effect.

Because some PPIs are known to be strong inhibitors of CYP2C19 activity, it is reasonable to believe that PPI may reduce the clinical response to clopidogrel. Controversy remains over whether this treatment interaction is clinically meaningful.

In November 2009, the U.S. Food and Drug Administration (FDA) issued a warning that concomitant use of omeprazole and clopidogrel should be avoided and that other drugs that reduce stomach acid do not interfere with the anti-clotting activity of clopidogrel. The European Medicines Agency (EMEA) extended the warning to discourage concomitant use of all PPIs unless absolutely necessary. These recommendations were based on pharmacokinetic/pharmacodynamic and observational studies. Well-performed studies have shown that the mean plasma concentration of the clopidogrel active metabolite is lower in patients treated with omeprazole in combination with clopidogrel than in patients treated with clopidogrel alone, also with a 600-mg loading and 150-mg maintenance dose. Pharmacodynamic studies have confirmed the reduction of platelet reactivity.

Whether treatment with PPIs affects cardiovascular outcome in patients receiving clopidogrel has been unclear. Several small observational studies showed a significant association between PPI use and cardiovascular risk, whereas propensity-matched studies and substudies of large randomized trials such as the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 and the Platelet

Inhibition and Patient Outcomes (PLATO) study revealed no association. A recently performed meta-analysis including 159,138 patients from 25 studies found an association of PPIs with reduction in gastric bleeding events and a higher risk of stent thrombosis but no association with the risk of death. One randomized trial, the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT), studied the effect of omeprazole versus placebo in patients treated with dual antiplatelet therapy. Although the trial was stopped prematurely for financial reasons, 3,637 patients were enrolled. The trial showed a 66% relative reduction in gastrointestinal events but no effect of omeprazole on cardiovascular events.

In summary, the totality of data suggests that a pharmacokinetic and pharmacogenetic clopidogrel–PPI interaction via CYP2C19 is real but that concomitant use of PPIs has minimal or no clinical consequence in low–medium-risk patients on long-term treatment. A small but clinically meaningful interaction with PPI in ACS patients at high ischemic risk in the acute settings cannot be excluded. Treatment with other potent $P2Y_{12}$ receptor inhibitors, such as prasugrel and ticagrelor, is not associated with an interaction with PPIs and could be considered in patients at high risk for ischemic events. In patients at risk for peptic ulcer, treatment with effective gastric protection, including PPIs, should not be withheld.

New antiplatelet agents under development

Current management of ACS includes risk stratification by clinical findings and the use of electrocardiographic and biochemical markers. It is recommended that all patients with an established diagnosis of ACS receive immediate antithrombotic treatment with dual platelet inhibition (aspirin and a $P2Y_{12}$ inhibitor) plus intravenous or subcutaneous anticoagulation. In addition, patients should also receive beta-blockers, statins, and, frequently, angiotensin-converting enzyme (ACE) inhibitors. The majority of patients hospitalized for ACS are rapidly admitted to a catheterization laboratory for identification of the culprit lesion, followed by balloon dilatation and stenting if feasible. At discharge, it is generally recommended that patients receive long-term secondary prevention with a combination of aspirin, beta-blockers, statins, ACE inhibitors, and $P2Y_{12}$ inhibitors for at least 1 year. However, despite these measures, there is still a 10% risk of death, reinfarction, or stroke during the year following discharge. The magnitude of this risk varies among patient populations, with the highest risk in older patients and those with diabetes mellitus, previous myocardial infarction (MI), cardiac or renal dysfunction, manifestations of atherosclerotic disease, or multi-vessel coronary artery disease (CAD). If current therapeutic approaches for ACS are to be improved, greater focus will be needed on these high-risk groups.

New therapies currently under development aim to prevent further progression of thrombosis and atherosclerosis and to correct underlying metabolic disturbances (e.g., diabetes and dyslipidemia). The primary challenge in preventing and managing ACS, both now and in the future, will be to tailor treatments for each patient, taking into consideration patient characteristics, comorbidities, underlying short- and long-term risk factors, and expected individual responses to different medications. These ambitions will likely place a substantial burden on global health care resources and may ultimately require prioritization among several treatment alternatives.

Platelet inhibition has been a mainstay in the prevention of MI and death in patients with ACS for approximately 20 years. Aspirin therapy yields consistent inhibition of platelet thromboxane A_2 release. However, inhibiting this pathway only modestly attenuates platelet activation without any influence on ADP-induced platelet activation. Aspirin treatment reduces the relative risk of MI and death by 30–50% compared with placebo in patients with ACS. However, aspirin alone has no convincing effect on prevention of stent thrombosis. Therefore, other pathways need to be inhibited in the highly prothrombotic environment of ACS. The $P2Y_{12}$ receptor plays a major role in the ADP-mediated amplification of platelet response regardless of the stimulus. Clopidogrel and prasugrel are thienopyridine pro-drugs acting on this receptor by almost identical active metabolites that irreversibly bind to the receptor. Slow and variable active metabolite generation leads to clopidogrel having a slow onset of action and wide inter-individual variability in pharmacodynamic response. However, as shown in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, compared with aspirin alone, clopidogrel provided a relative 20% reduction in death, MI, or stroke at a median of 9 months of treatment. Despite variability in platelet responsiveness, the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS) 7 trial—a 2×2 factorial randomized comparison of standard-dose (300 mg load/75 mg daily) versus higher-dose (600 mg load/150 mg daily for 6 days, then 75 mg daily) clopidogrel and lower-dose (75–81 mg) versus higher-dose (325 mg) aspirin treatment—failed to show superiority for the higher-dose clopidogrel regimen. However, in a subgroup analysis of PCI-treated patients, there was a substantial reduction in stent thrombosis in patients treated with the higher-dose clopidogrel regimen.

Generation of the active metabolite of prasugrel is more efficient than for clopidogrel, resulting in more rapid onset

of action, more pronounced platelet inhibition, and no clinically important variability in response. In the setting of these pharmacokinetic and pharmacodynamic features, prasugrel treatment resulted in a 20% reduction in death, MI, or stroke and a halving of the risk of stent thrombosis compared with clopidogrel in the TRITON-TIMI 38 trial of patients undergoing a planned PCI procedure. However, both the addition of clopidogrel to aspirin and the use of prasugrel instead of clopidogrel were associated with significant increases in major bleeding in CURE and TRITON-TIMI 38, respectively.

Ticagrelor, the first reversibly binding oral $P2Y_{12}$ receptor antagonist, does not require metabolic activation, has a rapid onset of action, and can disassociate from the receptor, permitting restoration of platelet function without the need for production of new platelets. In pharmacodynamic studies, ticagrelor demonstrated greater, more rapid, and more consistent ADP-induced platelet inhibition compared with clopidogrel and more rapid offset of action following cessation of therapy. In the PLATO study, 18,624 patients with ACS were randomized within 24 h after symptom onset to ticagrelor versus clopidogrel. The results showed a 16% relative reduction of the composite of cardiovascular death, MI, or stroke, a 22% reduction in total mortality, and a 33% reduction in definite stent thrombosis. Ticagrelor was not associated with an increase in overall bleeding, but, during long-term treatment, there was more non-procedural bleeding with ticagrelor.

Currently, elinogrel, a reversibly binding competitive $P2Y_{12}$ receptor antagonist for both intravenous and oral administration, is under evaluation. In a recently presented phase II trial (Novel Intravenous and Oral P2Y12 Inhibitor in Non-Urgent PCI [INNOVATE-PCI]), elinogrel was associated with a slight dose-related increase in total bleeding without a clear signal for reduction in ischemic events compared with clopidogrel.

Other targets for platelet inhibition are also under investigation (e.g., the protease-activated receptor 1 [PAR-1]). Preclinical and phase II studies suggest that consistent and high levels of PAR-1 inhibition may have a beneficial antithrombotic effect with minimal increase in bleeding. Phase III studies of the selective PAR-1 inhibitor, vorapaxar, are currently underway, both in ACS and chronic CAD.

In conclusion, several new alternatives providing more rapid and consistent platelet inhibition than clopidogrel are currently being explored for routine treatment of patients with ACS. These new treatments seem to provide additional benefits to the patients without unacceptable increases in the risk of bleeding if used appropriately. Within the next few years, even more treatment alternatives might be available to further improve outcomes of the large patient population with ACS.

Novel parenteral anticoagulants

Despite its limitations, unfractionated heparin (UFH) remains a commonly used parenteral anticoagulant in clinical practice. The major limitations of UFH include an unpredictable pharmacodynamic response, associated off-target effects, and the need for pharmacodynamic monitoring. Lack of pharmacologic specificity is another limitation. As such, the scientific community has moved toward using novel anticoagulants that target singular proteases within the coagulation system.

Bivalirudin, a direct thrombin inhibitor with a short circulating half-life, has recently shown good clinical efficacy with less bleeding compared with either UFH or LMWH. The synthetic pentasaccharide, fondaparinux, is a specific, indirect inhibitor of factor Xa. Despite, the convenience of a once-a-day subcutaneous injection for the management of patients with ACS, the need for supplemental UFH during transition to the catheterization laboratory limits its wider adoption in clinical practice. Concerns also remain over the propensity for equipment-associated thrombosis, as well as the absence of a reliable antidote to reverse its anticoagulant effect. Another factor Xa inhibitor, otamixaban, has demonstrated early safety as a parenteral anticoagulant in the catheterization laboratory; in the phase II Otamixaban in Comparison to Heparin in Subjects Undergoing Non-Urgent Percutaneous Coronary Intervention (SEPIA-PCI) trial, equipment-associated thrombosis occurred at a similar rate in both otamixaban and UFH-treated patients.

In response to existing limitations of approved parenteral anticoagulants, REG1 was designed to achieve rapid inhibition of factor IXa with active, antidote-mediated reversibility. This drug-antidote construct is now undergoing late phase II testing in patients with ACS.

Vitamin K antagonists

The vitamin K antagonists (VKAs) have been the only anticoagulants available for oral use since their first administration to a patient more than 50 years ago. The mechanism of action of this drug class is complex; they achieve their anticoagulant effect by inducing the synthesis of dysfunctional forms of factors II, VII, IX, and X. The target of VKAs is the enzyme vitamin K epoxide reductase (VKOR). Single nucleotide polymorphisms in the gene that codes for this enzyme (as well as single-nucleotide polymorphisms [SNPs] in the genes that encode CYP2C9) can render the patient more (or, in some cases, less) sensitive to warfarin; thus, common genetic variations, along with factors such as sex, age, and weight, lead to significant (and sometimes unpredictable) inter-individual variability in the

dose required to achieve the targeted anticoagulant effect. Even patients whose dose has been determined through titration and adjustment can experience clinically relevant sudden changes in their anticoagulant effect because of interactions with diet (mostly due to variation in vitamin K intake) or other medications (especially drugs that interact with the cytochrome P450 system). These features, along with the narrow therapeutic index, slow onset, and long pharmacodynamic half-life characteristic of VKAs, have created challenges for clinicians and patients alike.

Despite the undesirable attributes of VKAs, they have proven to be extremely effective in the prevention of AF-related stroke, recurrent venous thromboembolism (VTE), and other unwanted clinical events. Recently, the inconvenience of VKAs has been reduced by the opportunity for patient self-testing, but self-testing does not necessarily make VKAs safer or more effective than they are in the context of a dedicated system of anticoagulation management. Indeed, the safety of VKAs has improved with the advent of dedicated anticoagulation management services and the application of evidence-based strategies to reverse the VKA anticoagulant effect in bleeding patients. Going forward, it is likely that VKA use will decrease, but not disappear, once new oral anticoagulant agents become available.

ACS with ST-segment elevation: guidelines perspective on antithrombotic therapy

Many anticoagulants and antiplatelet agents are now available for the treatment of ACS patients. In patients with ST-segment elevation MI (STEMI) undergoing primary PCI, clopidogrel and UFH or bivalirudin (a direct antithrombin agent) are the most frequently used agents. For patients treated with lytic therapy, UFH, enoxaparin, and fondaparinux (with streptokinase only) are used as anticoagulant co-therapy. Clopidogrel is also given routinely with lytic agents to patients under age 75 years. No reliable data are available in patients aged >75 years.

Clopidogrel is widely used as an adjunctive therapy for primary PCI and has also been shown to be beneficial in patients treated with fibrinolytic therapy (Clopidogrel as Adjunctive Reperfusion Therapy [CLARITY] study; Clopidogrel and Metoprolol in Myocardial Infarction Trial [COMMIT/CCS-2]). However, its limitations—particularly slow onset of action, variability in response, and irreversible binding to the P2Y12 receptor—create challenges for STEMI care. Prasugrel, approved for use in Europe in 2009 and in the U.S. in 2009, is a third-generation thienopyridine and has a similar mechanism of action to clopidogrel but superior pharmacokinetic characteristics. The greater efficacy of prasugrel over clopidogrel in the TRITON-TIMI 38 trial was particularly evident in patients with STEMI, all of whom underwent primary PCI. However, prasugrel was associated with an increased risk of major bleeding, although in the STEMI population, there was no increase in life-threatening bleeding compared with clopidogrel.

Several novel antiplatelet therapies are currently in clinical development or have only recently been approved. The PLATO study demonstrated that ticagrelor reduced the incidence of death, MI, or stroke by 16% and of cardiovascular death by 22% compared with clopidogrel in STEMI patients. With ticagrelor, there was an increased risk of non-coronary artery bypass graft (CABG) bleeding complications. Also, cangrelor is an intravenous, fast, direct-acting, and reversible $P2Y_{12}$ inhibitor. No significant differences with clopidogrel could be demonstrated in ACS patients in the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI trial.

It is likely that prasugrel and ticagrelor will be recommended in the guidelines for STEMI patients undergoing primary PCI. Because these agents have not been tested prospectively with lytic agents, clopidogrel will remain the recommended ADP antagonist with lytic therapy.

Obviously, there is no role for new oral anticoagulants such as rivaroxaban and apixaban in the acute reperfusion phase of STEMI. Whether these agents may prevent recurrent ischemic events afterwards is unknown.

Antithrombotic therapy in ACS with non-ST-segment elevation

There are three antithrombotic agents to choose from: enoxaparin, fondaparinux, and bivalirudin. All have been shown to be superior to UFH. However, there are a number of considerations in choosing an antithrombotic agent for non-ST-segment elevation ACS. These include ischemic risk, bleeding risk, whether an invasive or conservative strategy will be employed, time to catheterization (<12 h vs. >12 h), whether drugs will be switched, whether the patient is aged <75 or ≥75 years, and the patient's renal function.

Major bleeding is strongly associated with subsequent mortality and ischemic events and, many believe, is at least as important as reinfarction. Most bleeding complications are iatrogenic, attributable to femoral artery access for PCI, and related to the use of potent antiplatelet and antithrombin medications. The incidence of bleeding is affected by the choice of anticoagulant and overdosing.

Enoxaparin has been shown in trials of over 22,000 patients to reduce death and MI by 20% and to have similar outcomes as compared with UFH when a conservative strategy is employed, but its use is associated with a modest increase in bleeding when an invasive strategy is employed.

There is also a large clinical experience for bivalirudin in non-ST-segment elevation ACS. Over 20,000 patients have been randomized in trials showing that major bleeding is reduced by about 50% with no increase in ischemia compared with UFH.

Crossover of antithrombotics

The patients in the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial who crossed over between UFH and enoxaparin had an increase in bleeding complications. Crossover occurred at various times through the study period, at times in response to clinical or clinician perception. In a secondary analysis from this study, results indicated a significant association between crossover from enoxaparin to UFH and TIMI bleeding but not in the other direction, and no crossover association was found in death or MI.

Switching from UFH or enoxaparin to bivalirudin in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial was not associated with an increased risk for ischemic events. Furthermore, switching to bivalirudin provided patients with a 50% reduction in bleeding.

Fondaparinux is an indirect factor Xa inhibitor tested against enoxaparin in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial. The ischemia rate was similar to UFH, but severe bleeding complications were significantly reduced with fondaparinux, and long-term mortality and stroke rates were also reduced. Because of a higher rate of catheter thrombosis when fondaparinux alone is used, UFH (85 μ/kg) should be added for patients undergoing PCI.

If there is a very high risk of ischemia, bivalirudin is recommended, or UFH with a IIb/IIIa antagonist added if there is angiographic thrombosis or poor TIMI flow. If there is a low-to-high risk of ischemia, all four agents (fondaparinux, LMWH, UFH, and bivalirudin) are good choices. Bivalirudin is an attractive option if there is an increased risk of bleeding and an early invasive strategy is planned. Fondaparinux is a good option if a conservative strategy is planned.

A number of different anticoagulant strategies can be appropriately selected based on individual risk stratification for ischemia and bleeding.

Biomarkers of thrombosis: where do we stand in 2010?

From a clinical perspective, biomarkers serve three main purposes: to diagnose or exclude a disease diagnosis; to provide information about prognosis or to risk stratify; and, most elusively, to guide treatment decisions. Pulmonary embolism (PE) and acute MI are two acute thrombotic disease entities, often presenting with similar symptoms, for which clinically useful biomarkers of thrombosis have evolved across each of these three domains.

Pulmonary embolism is first classified as high or intermediate/low risk based on hemodynamic and respiratory status. For those who are stable (i.e., intermediate/low risk), the biomarker, D-dimer, is used to exclude the diagnosis of PE and to guide further imaging and/or treatment. Given its exquisite sensitivity, despite low specificity, its negative predictive value is very high, such that further work-up with imaging or treatment is not necessary if the D-dimer concentration is low.

Troponin remains the gold standard for establishing a diagnosis of MI in the setting of clinical symptoms of ischemia. Troponin assays are more sensitive and more specific for myocardial injury than creatine kinase (CK)-MB. However, the increasing clinical availability of high-sensitivity troponin assays that can detect circulating troponin at levels well below the 99th percentile of a normal reference population and can also achieve 10% coefficient of variation (CV) at the 99th percentile is challenging the diagnostic utility of troponin testing for diagnosis of MI. However, the increased sensitivity of these assays is offset by reduced clinical specificity, resulting in low positive predictive value. For example, up to 70% of patients with heart failure, which often co-exists with coronary disease, may present with elevated troponin by high-sensitivity assays. The parameters for diagnostic use of these assays are still being discussed. However, these assays may be particularly useful in early diagnosis/triage in the emergency room, where elevations above the 99th percentile in MI patients are detectable much earlier than with standard assays. Given these challenges, heightened awareness of the relationship of pre-test probability with the occurrence of false-positive (and false-negative) diagnoses will be needed.

In the meantime, systematic efforts to increase the accuracy of physicians' clinical assessments of risk in patients with suspected ACS must be undertaken. In a study from the Canadian ACS 2 Registry, despite the availability of the 12-lead electrocardiogram (ECG) and results of assays for markers of myocardial necrosis, there was little relationship between physician-estimated risk category and that determined from available risk scores, with wide variability in these risk scores within the physician-estimated category. A better alignment between physician-estimated risk and systematically determined risk is critical as this study also showed that physicians, overall, treat patients whom they judge as being at higher risk more aggressively with both coronary procedures and medications.

Even with a systematic approach to risk stratification, novel or existing biomarkers may be useful in refining prognosis or guiding treatment selection. Many biomarkers of thrombosis and inflammation have been identified, but rarely have studies considered more than a few biomarkers simultaneously, and few have made the translation from biomarker of risk to biomarker for stratified application of treatments. Troponin testing is the cardiovascular biomarker that best exemplifies this feature. In studies mostly done with older assays, troponin identified high-risk populations that were most likely to benefit from glycoprotein (GP) IIb/IIIa inhibitors, LMWH, and a strategy of early angiography in patients presenting with non-ST-segment elevation ACS. Whether this will be true as high-sensitivity troponin assays become available, particularly for levels below the 99th percentile of current assays, remains to be seen.

The role of high-sensitivity C-reactive protein (hsCRP) in guiding therapy with statins recently has come under scrutiny. Although the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) showed that patients with normal low-density lipoprotein cholesterol (LDL-C) who had an hsCRP level > 2 mg/dl benefitted from treatment with rosuvastatin, there was no arm with similar LDL-C levels but hsCRP < 2 mg/dl. Thus, this trial cannot be used to argue that hsCRP should be used to guide statin treatment in primary prevention patients. Additionally, a recent cost-effectiveness analysis suggested that, assuming long-term safety of statins, availability of low-cost generic agents, and similar efficacy of statins in low-to-intermediate risk patients, treating men with statins without screening hsCRP would be cost-effective down to 50 years. At 70 years, using hsCRP to guide therapy would be cost-effective in both men and women; in both men and women, the lower bounds of age for primary prevention without hsCRP guidance rose with increasing numbers of cardiovascular risk factors.

As an example of the increasing interface of genetics with clinical care, there has been much interest in the use of genetic testing for the CYP2C19 mutation to guide clopidogrel therapy. However, despite associations of the mutation with outcome and demonstrated pharmacodynamic and pharmacokinetic variability with clopidogrel treatment according to carrier status, studies to date have not demonstrated that testing for this genetic mutation is useful in guiding treatment. A large randomized clinical trial, GRAVITAS, evaluated whether tailored clopidogrel dosing according to phenotypic platelet responsiveness measured prior to discharge after drug-eluting stent implantation would reduce thrombotic complications of stent implantation. Its results were presented at the 2010 Scientific Sessions of the American Heart Association (AHA) in Chicago and showed no benefit on cardiovascular outcomes or stent thrombosis with a double dose of clopidogrel in patients receiving drug-eluting stents with high residual platelet activity on the regular clopidogrel dose. These results are not yet published.

Thus, in 2010, it is increasingly evident that global risk assessment is needed to help clinicians align treatment with diagnosis and risk. Biomarkers play an important role in this process. However, rapid advances in assay technology and the increasing availability of new biomarkers generated from genomic discovery and applications of genetic testing create challenges that must be considered. Novel biomarkers must be systematic and rigorously evaluated, and their practical clinical utility must be demonstrated before they become part of a routine risk assessment strategy.

Measuring quality in ACS: where does antithrombotic therapy fit?

Quality of care has been defined as the "degree to which health care services increase the likelihood of desired health outcomes and are consistent with current professional knowledge." Simply put, this asks: Are we doing the right things (practicing evidence-based care); are we doing the right things right (delivering this care in a safe, skilled manner); and are our patients better off for it (are their outcomes improved)? When viewed in this manner, contemporary treatment of patients with ACS is challenged. Studies have consistently demonstrated an under-utilization of evidence-based therapies, as well as failure to provide such care in a safe and timely fashion. And while care is improving over time, consistent gaps remain. For example, 2010 data from the ACTION Registry®-Get With the Guidelines (GWTG)™ found that between 15 and 20% of eligible ACS patients fail to receive dual antiplatelet therapy acutely and at hospital discharge.

The standard application of evidence-based therapies, however, neglects to consider that these treatments ideally should be "personalized" for the individual patient. Antithrombotic therapies in ACS care effectively prevent recurrent ischemic events or, alternatively, cause iatrogenic bleeding. The balance between the benefits and risks is influenced by three domains. The first domain relates to features of the drug itself, including drug absorption, activation, potency, clearance, and interaction with other drugs. Patient factors represent a second domain influencing safety and efficacy of antithrombotic therapies in ACS, including such factors as patient age, sex, renal function, and presence of diabetes. These clinical features influence the baseline odds for recurrent ischemic events but also can affect the safety of antithrombotic therapy, either through

changing the drug's pharmacokinetic and dynamic properties or increasing the patient's underlying disposition to bleed (i.e., peptic ulcer disease).

Provider and system factors also influence the quality of care and subsequent outcomes in ACS. Studies have found that a number of patients in the United States receive the wrong dose of antithrombotic therapies. Combined, up to 20% of all bleeds in the United States are estimated to be caused by excessive antithrombotic therapies. The reasons for excessive drug dosing often relate to a failure to individualize dose based on body weight, age, or renal function.

While there are challenges to the effective and safe use of antithrombotic therapies in ACS, the world is changing, and efforts to improve the quality of ACS care delivered around the world abound. In particular, giving clinicians feedback on their care practices relative to those of their peers has been shown consistently to improve ACS quality of care. Moving forward, this follow-up and feedback regarding ACS practices must extend to consider longitudinal care and outcomes. For example, studies have consistently demonstrated that patients who discontinue dual antiplatelet therapy early after receiving a stent are at high risk for subsequent cardiac events. Importantly, patient compliance appears modifiable via patient education. Those who understand the reasons for their medications and the need for continued use have higher rates of compliance.

In the future, both providers and patients will have increasing access to electronic tools to facilitate better ACS care. These include electronic order entry systems that will support wiser drug choices and prevent medical errors related to drug dosing. We will also see the evolution of community systems of care that will encourage appropriate triage of ACS patients to support more timely ACS care. Finally, we will see the evolution of patient health records that will support a new collaborative model of care between patients and their caregivers.

Antiphospholipid syndrome

Antiphospholipid syndrome is widely recognized but incompletely understood. There are five areas worthy of consideration: pathophysiology, epidemiology, clinical manifestations, diagnosis, and management. The pathophysiology of antiphospholipid syndrome involves production of IgG antibodies against beta 2-glycoprotein I on the surface of vascular endothelial cells. The antibodies cause expression of adhesion molecules and up-regulation of tissue factor production. In addition, they produce up-regulation of tissue factor within monocytes, expression of GP IIb/IIIa receptors on platelets, and increased thromboxane A2 synthesis. The interaction of antibodies with coagulation regulatory proteins such as activated protein C in combination with complement activation and inflammation establishes a highly prothrombotic state. The available evidence suggests that an existing thrombophilia in antiphospholipid syndrome can be exaggerated acutely as part of a putative "second hit" phenomenon following trauma, infection, and other conditions in which a prothrombotic environment rapidly develops.

Antiphospholipid antibodies are detected in 20% of patients with an ischemic stroke before age 50 years, 20% of patients with VTE, 10–15% of women with recurring miscarriages, and 20% of women with a diagnosis of preeclampsia. The most common clinical manifestations of antiphospholipid syndrome, occurring in >20% of individuals, include VTE, thrombocytopenia, miscarriage or fetal loss, ischemic stroke or transient ischemic attack, migraine headache, and livedo reticularis. Less common clinical manifestations, occurring in 10–20% of individuals, include heart valve abnormalities, hemolytic anemia, and accelerated CAD. Unusual clinical manifestations, occurring in <10% of individuals, include seizures, vascular dementia, retinal artery or vein thrombosis, pulmonary hypertension, skin ulcers with digital gangrene, osteonecrosis, renal insufficiency, and mesenteric ischemia.

The diagnosis of antiphospholipid syndrome is supported by clinical criteria, including vascular thrombosis involving one or more episodes of arterial, venous, or small-vessel thrombosis in any tissue or organ. Thrombosis should be present without substantial evidence of inflammation within the vessel wall. A diagnosis of antiphospholipid syndrome in the context of pregnancy is supported by at least one of the following criteria: one or more unexplained deaths of a morphologically healthy fetus at or beyond the 10th week of gestation; one or more premature births of a morphologically healthy new born before the 34th week of gestation either because of eclampsia or severe preeclampsia; or at least three unexplained consecutive spontaneous abortions before the 10th week of gestation, with anatomical or chromosomal abnormalities having been excluded.

The laboratory diagnosis of antiphospholipid syndrome includes the following: detection of a lupus anticoagulant on two or more occasions at least 12 weeks apart; anticardiolipin antibody of IgG or IgM subtype, or both in serum or plasma, present in medium or high titers on at least two or more occasions at least 12 weeks apart measured with a standardized ELISA; or anti-beta 2 GP1 antibody of IgG or IgM subtype, or both in serum or plasma, at medium or high titers on at least two or more occasions at least 12 weeks apart.

The management of patients with antiphospholipid syndrome includes a strategy of primary prophylaxis,

where patients with systemic lupus erythematosus and a circulating lupus anticoagulant or persistently positive anticardiolipin antibody titer would receive hydroxychloroquine either alone or in combination with low-dose aspirin. Patients with obstetric antiphospholipid syndrome are traditionally treated with low-dose aspirin, while asymptomatic carriers of antiphospholipid antibodies do not typically require therapy. However, it is important to emphasize that all patients with antiphospholipid antibodies likely benefit from strict control of vascular risk factors and should receive adequate thromboprophylaxis in high-risk situations such as surgery, the post-partum period, and during prolonged periods of immobilization. Management of patients with antiphospholipid syndrome without previous thrombosis but recurring early (pre-embryonic or embryonic) miscarriages should include either low-dose aspirin alone or in combination with either UFH or LMWH. Patients with antiphospholipid syndrome without previous thrombosis but with prior fetal death at more than 10 weeks gestation or early delivery (<34 weeks gestation) due to severe preeclampsia or placental insufficiency should be treated with UFH or LMWH throughout pregnancy.

Secondary prophylaxis of patients with antiphospholipid syndrome and prior thrombosis typically includes indefinite anticoagulation with warfarin, titrated to a target INR of 2.5 (range 2.0–3.0). There is a suggestion that patients with a prior arterial thrombotic event should be targeted to a higher INR (3.5; range 3.0–4.0) or warfarin titrated to a target INR of 2.5 plus low-dose aspirin. The latter two strategies have also been used for patients with recurring events despite warfarin anticoagulation.

The potential use of newer-generation anticoagulants, such as oral direct factor Xa or direct thrombin inhibitors, will require further evaluation.

Venous thromboembolism prophylaxis in surgical patients

Venous thromboembolism is the most preventable cause of morbidity and mortality in postoperative settings; it is the second most common medical complication, the third most common source of excess health care resource utilization, and the third most common cause of mortality in postoperative patients. Accordingly, pulmonary embolism is the most common yet preventable cause of death.

Proximal vein VTE presents the highest risk for PE: 50% asymptomatic or ''silent'' PE and 25% of distal vein VTE will extend to proximal veins within 1 week of presentation. Most postoperative cases of VTE are clinically silent: 2–30% of in-hospital postoperative deaths are attributable to PE.

Over 30 million operations are performed annually in the United States, and the incidence of postoperative VTE without prophylaxis is 10–20% for low-risk and up to 80% in high-risk patients. The rates of fatal PE in the highest-risk patients range from 0.5 to 30%, with length of hospital stay of 5.4 days, excess mortality of 6.6%, and costs reaching $25,000 more than compared with controls.

There were approximately 38 million discharges in the United States in 2006: 7 million were surgical inpatients. According to American College of Chest Physicians (ACCP) Antithrombotic and Thrombolytic Guidelines risk categories, 44% of these patients were at low risk for VTE; 15, 24, and 17% were at moderate, high, and very high risk, respectively. Risk assessment strategy and systematic computerized electronic alerts should be a combined objective to increase the use of VTE prophylaxis and to reduce the rates of symptomatic VTE among hospitalized patients.

For prevention of this common problem, new evidence is available to support novel anticoagulant therapy.

Rivaroxaban

Evidence for this oral, direct factor Xa inhibitor for thromboprophylaxis was presented in the results from the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) 1, 2, 3, and 4 trials (Table 1). The RECORD 1 trial was designed to evaluate oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty. The primary outcome was total VTE: any deep vein thrombosis (DVT), non-fatal PE, and all-cause mortality at 36 days (range 30–42); secondary outcomes included major VTE: proximal DVT, non-fatal PE, and VTE-related death. DVT included any, proximal, distal, and symptomatic VTE.

In the RECORD 2 trial, extended thromboprophylaxis with oral rivaroxaban versus short-term subcutaneous enoxaparin following total hip replacement was evaluated. The main study question was whether extended-duration prophylaxis was superior to short-duration prophylaxis. In summary, RECORD 2 showed that extended-duration prophylaxis was superior to short-duration prophylaxis and that rivaroxaban provided an effective option for such a strategy and had a good safety profile.

Finally, RECORD 3 and 4 evaluated thromboprophylaxis after total knee arthroplasty and found that rivaroxaban (10 mg once a day for 10–14 days), given in a fixed, once-daily dose regimen without coagulation monitoring, was superior to enoxaparin (40 mg once a day for 10–14 days) in preventing venous thrombosis with similar rates of bleeding.

Table 1 Main efficacy outcomes of the RECORD trials

Trial	Setting	Enoxaparin regimen	Rivaroxaban regimen	DVT/PE/death (%)	RRR (%)	Symptomatic VTE (%)	RRR (%)
RECORD 1, $n = 4{,}541$	Hip arthroplasty	40 mg qd, 35 d	10 mg qd, 35 d	3.7 vs. 1.1	70	0.5 vs. 0.3	NS
RECORD 2, $n = 2{,}509$	Hip arthroplasty	40 mg qd, 10–14 d	10 mg qd, 31–39 d	9.3 vs. 2.0	79	1.2 vs. 0.2	80
RECORD 3, $n = 2{,}531$	Knee arthroplasty	40 mg qd, 10–14 d	10 mg qd, 10–14 d	18.9 vs. 9.6	49	2.0 vs. 0.7	66
RECORD 4, $n = 3{,}148$	Knee arthroplasty	30 mg bid, 10–14 d	10 mg qd, 10–14 d	10.1 vs. 6.9	32	1.2 vs. 0.7	NS

Bid twice daily; *d* days; *NS* not significant; *qd* daily; *RRR* relative risk reduction

Apixaban

Apixaban, an oral, direct factor Xa inhibitor, was evaluated for DVT prophylaxis after total knee replacement in a phase II dose-ranging study. Aggregated apixaban doses resulted in a 21% ($P < 0.02$) reduction in VTE and all-cause death compared with enoxaparin and a 53% ($P < 0.01$) reduction compared with warfarin. Major bleeding event rates were low (0–3.3%) and comparable across all apixaban arms and the enoxaparin and warfarin groups. Similar results were shown in a dose-ranging trial for the treatment of DVT.

The phase III, randomized, double-blind Apixaban Dose Orally versus Anticoagulation with Enoxaparin (ADVANCE)-1 trial compared the efficacy and safety of 2.5 mg oral apixaban twice daily to subcutaneous 30 mg enoxaparin for the prevention of VTE after total knee replacement in 3195 patients. The primary outcome rates in each arm were similar (8.99% vs. 8.85%). The predetermined non-inferiority end point was not met, but event rates were comparable, and there was less clinically relevant bleeding in the apixaban arm. There was no difference between the two groups in serious adverse events.

The Apixaban Dose Orally versus Anticoagulation with Enoxaparin (ADVANCE)-2 trial compared apixaban (2.5 mg orally twice daily) with enoxaparin (40 mg subcutaneously daily) for preventing VTE after total knee replacement. The primary efficacy outcome (all VTE) occurred in 15.1% of patients in the apixaban group and 24.4% in the enoxaparin group. A nonsignificant trend toward less clinically relevant bleeding also favored apixaban (3.5 vs. 4.8%, $P = 0.09$).

The Apixaban Dose Orally versus Anticoagulation with Enoxaparin (ADVANCE)-3 trial evaluated the efficacy and safety of oral, twice-daily apixaban 2.5 mg compared with subcutaneous enoxaparin 40 mg once daily in patients undergoing elective total hip replacement surgery. In this study, the primary efficacy end point occurred in 1.4% of patients in the apixaban group and 3.9% of patients in the enoxaparin group, demonstrating a statistically significant relative risk reduction for apixaban of 64% ($P < 0.001$ for non-inferiority and superiority). The safety outcome of major bleeding occurred in 0.8% of patients who received apixaban and in 0.7% of patients who received enoxaparin ($P = 0.54$). There was no difference between the two groups in serious adverse events.

Dabigatran

In patients undergoing total hip replacement who were enrolled in the Dabigatran Etexilate Compared with Enoxaparin in Prevention of VTE Following Total Hip Arthroplasty (RE-NOVATE) trial, both doses of the oral direct thrombin inhibitor, dabigatran etexilate, given for a median of 33 days were as effective as enoxaparin for the prevention of VTE, with a similar safety profile. Furthermore, dabigatran etexilate proved to be non-inferior to enoxaparin, when administered for the same duration, for reducing the risk of total VTE and all-cause mortality after total hip replacement. In patients undergoing total knee replacement who were enrolled in the Thromboembolism Prevention after Knee Surgery (RE-MODEL) trial, both doses of the oral direct thrombin inhibitor dabigatran etexilate, given for 6–10 days, were as effective as enoxaparin for the prevention of VTE, with a similar safety profile. Dabigatran etexilate proved to be non-inferior to enoxaparin (40 mg daily started the night before surgery) for the prevention of VTE after total knee replacement.

Should patients with cancer receive primary VTE prophylaxis?

Patients with cancer are at high risk for VTE, which is the cause of death in many patients with advanced malignancy. The risk for developing VTE is highest during the first 3 months after diagnosis and depends on many factors, including the use (and type) of chemotherapy as well as the

site and stage of the neoplasm. Recent randomized trials have confirmed the hypothesis that anticoagulants, especially when administered in therapeutic doses, can reduce the risk of VTE in at-risk cancer patients. Unfortunately, the absolute risk reductions achieved in several of the trials reported to date have been small and do not justify the hazards and costs associated with a strategy of routine prophylaxis in all patients. For example, the Prophylaxis of Thromboembolic Events in Cancer Patients Receiving Chemotherapy (PROTECHT) study enrolled 1,150 patients with advanced lung, breast, or colon cancer (all were receiving chemotherapy) and randomly assigned them to either nadroparin (prophylactic dose) or placebo. Although the proportion of patients experiencing the primary end point was lower in the treatment group (2.1 vs. 3.9%, $P = 0.033$), this small risk difference has not resulted in the adoption of primary prevention strategies for these populations. The PROTECHT results indicate that 55 patients would have to be treated with LMWH for 1 year to prevent one thromboembolic event.

At least two trials that have recruited patients with pancreatic cancer receiving gemcitabine (and that compared therapeutic-dose LMWH to placebo) have demonstrated more dramatic risk reductions for VTE but did not clearly show a survival advantage and have yet to be published in full manuscript form. Several groups have now validated the risk prediction model of Khorana et al.—a scoring system that has demonstrated that the risk of developing VTE increases with a number of factors, such as elevated white blood cell or platelet count, increased body mass index, or decreased hemoglobin. However, the absolute VTE risk level at which practicing oncologists and their patients should consider primary prevention remains unclear and may change if/when oral anticoagulants are shown to be effective for this purpose. At this time, the National Cancer Center Network guidelines do not recommend routine use of primary VTE prophylaxis in any outpatient cancer population, except for patients with multiple myeloma who are receiving lenalidomide and dexamethasone.

Are there patients with PE who can be treated out of hospital?

Pulmonary embolism is a common condition affecting more than 1.5 million Americans yearly. It is a serious disease that accounts for 10% of all in-hospital deaths and is a major contributing factor in another 10% of deaths. Despite these elevated death rates, PE might be a more benign condition when associated with a lower thrombus burden. In this case, mortality is extremely low, and patients might be considered for outpatient therapy. Therefore, risk stratification is of utmost importance when considering therapy in PE.

Several risk stratification scores have been developed and include variables such as age, clinical status at hospital admission (heart rate, blood pressure, and respiratory rate), presence of cancer, and hypoxemia ($SatO_2 < 90\%$). The commonly used Geneva risk score demonstrates good discrimination for the prediction of death, major bleeding, and recurrent VTE at 3 months. Patients stratified as low risk (80% of total) have a 2.2% event rate, whereas high-risk patients have increased risk of complications (26%). Another famous score called PESI (Pulmonary Embolism Severity Index) performs similarly for the prediction of the same end points. More recently, echocardiographic data and biomarker measurements, such as cardiac troponins (cTnT and cTnI) and brain natriuretic peptide (BNP), have been included in these scores. Biomarkers predict death and other complications following PE with an odds ratio as high as 17.9 according to some studies. They also improve discrimination beyond clinical and echocardiographic variables. In conclusion, patients admitted with PE are at different risk. Currently available risk stratification scores help predict complications and enable the choice of the most suitable therapy for each patient. A study from the Netherlands presented as a late-breaking session at the American Society of Hematology annual meeting in December of 2010 indicates that out-of-hospital therapy may be reasonable in selected patients with PE.

Approaches for patients with venous thrombosis in unusual sites

The vast majority of proven episodes of DVT occur in the deep veins of the legs. When they occur in the proximal veins, embolization may travel to the lungs, producing PE. DVT and PE are often described as VTE and comprise a leading cause of hospital-acquired morbidity and mortality.

Venous thrombosis may occur in any vein. Recently, the frequency of DVT in non-leg veins has increased dramatically due to the increased sensitivity of our radiologic investigations. For example, improved resolution of abdominal ultrasonography and contrast-enhanced computed tomography (CT) scanning has led to a rapid increase in the frequency of detection of splanchnic venous thrombosis, oftentimes occurring in patients with minimal or no referable symptoms who are undergoing evaluation for unrelated medical indications. Cerebral vein thrombosis is a potentially devastating form of thromboembolism that is optimally detected with magnetic resonance venography or direct angiography. Again, due to the increasing availability and resolution of these modalities, the frequency of detection of these thrombi is increasing. Finally, DVT may

occur in other vascular sites such as the renal veins, pelvic veins, pulmonary veins, and in varicose veins located in any vascular distribution.

Thrombophilia testing is widely available and grossly overused. However, there appears to be a particular predilection for patients with selected forms of thrombophilia to develop thrombosis in unusual sites. For example, patients with paroxysmal nocturnal hemoglobinuria (PNH) appear to be particularly prone to develop Budd-Chiari syndrome, while patients with the JAK-2 mutation appear prone to splanchnic vein thrombosis. A recent systematic review demonstrated that almost one third of patients presenting with splanchnic venous thrombosis had the JAK-2 mutation, with many patients having a normal complete blood cell count. The JAK-2 mutation (although recently discovered) has traditionally been identified as being characteristic of myeloproliferative disorders. The mechanism by which this mutation predisposes a patient to splanchnic venous thrombosis is unknown. Both the lupus anticoagulant and anticardiolipin antibody are frequently detected in patients presenting with unusual forms of thrombosis, particularly at young ages. Detection of antiphospholipid antibodies, including both lupus anticoagulant and anticardiolipin antibody, is important because most experts would recommend extended-duration therapy with an oral anticoagulant in patients with these antibodies. There are no specific therapies for the JAK-2 mutation, and patients appear to be treated effectively with oral anticoagulants. Patients with PNH may be resistant to warfarin administered to a traditional INR between 2 and 3; recent studies have suggested a high rate of "warfarin failure." Eculizumab is a recently approved medication that blocks the terminal complement components and thus reduces hemolysis in patients with PNH. Indirect evidence suggests that this medication may also ameliorate the thrombotic complications of this disorder.

More common thrombophilias, such as the prothrombin gene mutation, appear to be particularly common in patients with cerebral vein thrombosis.

Ovarian vein and other pelvic vein thrombosis appear to be particularly common in the peripartum period. Renal vein thrombosis is particularly common in patients with renal cell carcinoma and may be more common in patients with nephrotic syndrome. DVT of the upper extremity is particularly common in the setting of indwelling central venous catheters and in athletes, presumably because of impingement on the veins leaving the arm during vigorous exercise.

Patients with unusual site thrombosis appear to respond to anticoagulation, with similar recurrence rates as patients with PE or thrombosis in the deep veins of the leg. Thus, a rapid-acting parenteral anticoagulant should be administered initially and overlapped with an oral VKA. This therapy may need to be modified as a result of studies of novel agents that may or may not require the initial course of parental anticoagulants.

There is no evidence as to how patients with "asymptomatic" clots should be treated. Most experts would treat patients with thrombi discovered in the setting of cancer or other high-risk situations. If there is reasonable evidence of prior thrombosis, then it may be reasonable to not anticoagulate. Patients who appear to be at high risk of complications, however, probably should be anticoagulated using a rapid-acting, parenteral anticoagulant overlapped with an oral VKA.

The duration of therapeutic anticoagulation has not been studied in these patients. Most experts extend anticoagulation because of a perception that recurrent disease could be associated with catastrophic complications. However, there is reasonable evidence that anticoagulants can be safely discontinued in selected patients, particularly in those with cerebral vein thrombosis.

In summary, DVT may occur in any vein. Thrombophilias appear to be particularly common in patients with unusual site thrombosis. Recent attention has focused on the JAK-2 mutation and PNH as causes of splanchnic and hepatic vein thrombosis, respectively. Anticoagulant therapy is indicated for all symptomatic patients. Optimal therapy of patients with screening-detected clots is unknown. In general, anticoagulant therapy is extended in patients with unusual site thrombosis due to the potentially catastrophic implications of recurrence.

Debate: VTE prophylaxis should be the default position for hospitalized medical patients—for/against

Thromboprophylaxis: the case against

There is no question that selected patients admitted to the hospital with medical disorders are at high risk of DVT and PE, oftentimes described as VTE. However, recommendations for the use of VTE prophylaxis have tended to err on the side of suggesting prophylaxis for most patients, despite a singular lack of evidence to support this recommendation. The ACCP guidelines recommend strongly that anticoagulant prophylaxis be provided to patients identified at high risk of VTE. Such patients include those with an extended duration of immobilization, congestive heart failure, serious thrombophilias, or those with more than one risk factor.

The case that VTE prophylaxis is not required in all patients is made simply. Patients with active bleeding or those perceived to be at very high risk of bleeding should not receive pharmacologic prophylaxis, thus establishing that there is a small but important subgroup of patients in whom prophylaxis is contraindicated. The bigger question

is whether VTE prophylaxis should be provided to low-to-moderate-risk patients.

Prophylaxis may be mechanical or pharmacologic. Mechanical prophylaxis can be active or passive. Passive mechanical prophylaxis, most commonly manifest as graduated compression stockings (GCS), are probably effective for the prevention of VTE but are significantly expensive when routinely used across a hospital and may be associated with transmission of infection. Intermittent pneumatic compression devices are probably more effective than passive compression devices, but they are expensive and are generally poorly used in hospitalized patients. Furthermore, reuse of intermittent compression device bladders may be associated with infectious diseases such as methicillin-resistant *Staphylococcus aureus*. There is no high-quality evidence by which to gauge the effectiveness of intermittent pneumatic compression devices in medically ill patients.

Pharmacologic prophylaxis generally consists of heparin or LMWH administered twice or three times daily. There is clear evidence that, in high-risk patients, pharmacologic prophylaxis reduces the risk of symptomatic DVT, PE, and fatal PE. However, there have been no studies demonstrating the effectiveness of these agents in the low-to-moderate-risk patient.

Irrespective of the indication, there is clear evidence that anticoagulants administered at prophylactic doses increase the risk of major bleeding. Major bleeding is expensive to treat and may be fatal in rare cases.

Modeling of the impact of prophylaxis provision on low-to-moderate-risk patients suggests that the risk of PE and fatal PE is low and very low, respectively. Although it is logical to assume that pharmacologic prophylaxis would further reduce the risk of thrombosis, there is also little doubt that prophylaxis would increase the risk of major and fatal bleeding. Rough modeling suggests, in fact, that, in low-risk patients, provision of prophylaxis would actually cause more fatal bleeding episodes than it prevented through reduced risk of PE. Additionally, the routine use of prophylaxis increases direct drug acquisition costs and dramatically increases the costs associated with the management of bleeding complications.

Based on the lack of evidence of efficacy, indirect but highly suggestive evidence of toxicity, a likely adverse cost-effectiveness profile, and the possibility that prophylaxis delivered to low-to-moderate-risk patients may actually increase the risk of death, it is clear that it is inappropriate to recommend VTE prophylaxis uniformly for medical patients.

Thromboprophylaxis: the case for

Pulmonary embolism is among the leading causes of death among patients hospitalized for acute medical illness. Although effective mechanical and pharmacologic modalities are available to reduce the risk of PE and DVT, clinicians often do not employ VTE prevention strategies for at-risk patients admitted with nonsurgical illnesses. The reasons for this underutilization of effective prophylaxis are not known with certainty; however, there are probably many factors involved. First, the physician caring for a patient with acute medical illness can easily be distracted by many other demands for his/her attention; VTE prevention can easily be forgotten. Second, a validated, user-friendly scheme by which medical patients can be stratified according to VTE risk does not exist. In light of the potential for "sensory overload" among inpatient physicians and the lack of an easy-to-use risk assessment model, it is unreasonable to expect health care providers reliably to prescribe prophylaxis against VTE to at-risk patients.

Cost is not a reason to oppose the routine use of VTE prevention strategies among medical patients. UFH and graduated compression stockings are relatively inexpensive, and there is high-quality evidence that both will reduce the risk of symptomatic DVT and PE. The absolute risk of major bleeding is not substantially increased by the use of low-dose anticoagulants (e.g., LMWH, fondaparinux, UFH) in this population. In other words, because of low baseline risk of bleeding in this population, it is likely that well over 100 patients would have to be treated with low-dose anticoagulants (versus nothing) to cause one additional major hemorrhage. While it would certainly be reasonable to withhold anticoagulants from a patient at high risk for bleeding (e.g., a cancer patient with profound thrombocytopenia), the "default" position should be to provide VTE prophylaxis to all medical patients because: 1) even patients at high risk for bleeding can benefit from mechanical interventions, and 2) for the vast majority of patients at "average" risk for bleeding, the trade-off will favor low-dose anticoagulants.

Triple therapy: patients with CAD and AF

Patients with cardiovascular disease may have several concomitant indications for antithrombotic therapy including ACS, DVT and PE, mechanical valves, AF, and coronary stent implantation. Overlapping indications for antithrombotic therapy may lead to the need for "triple therapy," defined here as aspirin, clopidogrel, and oral anticoagulation.

As the population ages, more patients will have both ACS and AF; accordingly triple therapy may be used more frequently. Prior studies have shown that, with more antithrombotic therapy, risk of bleeding increases. Many antiplatelet and anticoagulant drugs are part of the foundation for treatment of ACS and AF, making the decision

about the right combination of these agents challenging. However, limited evidence is available to guide therapeutic decision-making about triple therapy. Registry information, subgroup analyses from clinical trials, and overviews of single-center experiences have been published, but no randomized trials evaluating different strategies of triple therapy have been completed.

Multiple guidelines and consensus statements from national societies provide recommendations for clinicians concerning the use of triple therapy. A simple flow diagram can be used by physicians to guide decisions about the need for dual antiplatelet therapy or triple therapy based on the assessment of patient bleeding and stroke risk. Five additional factors should be considered: 1) use of the lowest dose of antiplatelet therapy; 2) use of bare metal stents versus drug-eluting stents to minimize the duration of antiplatelet therapy; 3) optimal INR within a range of 2.0–2.5; 4) gastric protection with PPIs; and 5) minimization of the duration of triple therapy. It is also important to re-evaluate regularly the need for triple therapy. The risk of stent thrombosis will decrease over time, whereas bleeding risk will remain constant.

Two ongoing randomized clinical trials will evaluate the role of triple therapy: the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) study of $\sim$ 500 patients post-stenting randomized to triple therapy versus dual therapy (clopidogrel and an oral anticoagulant) and the Intracoronary Stenting and Antithrombotic Regimen: Testing of a Six-Week Versus a Six-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting (ISAR-Triple) trial of $\sim$600 patients post-drug-eluting stent implantation randomized to triple therapy for 6 weeks versus triple therapy for 6 months.

Several new antiplatelet and anticoagulant agents are also being studied for ACS and AF, including the PAR-1 inhibitors in the Thrombin Receptor Antagonist for Clinical Events Reduction (TRACER) and TRA-2P programs; factor Xa inhibitors in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 46 (ATLAS ACS-TIMI 46) and the Apixaban for Prevention of Acute Ischemic Events (APPRAISE)-2 ACS trials; and factor Xa inhibitors in the Global Study to Assess the Safety and Effectiveness of DU-176b versus Standard Practice of Dosing with Warfarin in Patients with Atrial Fibrillation (ENGAGE AF-TIMI 48), Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE), and the Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation (ROCKET AF) trials. The future will be interesting. Triple therapy may actually be redefined in the future with new $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor, oral factor Xa inhibitors, and antithrombin agents. Indeed, warfarin may become obsolete in patients with ACS and AF. In addition, triple therapy may be replaced by "quadruple therapy" with aspirin, the $P2Y_{12}$ inhibition, PAR-1 inhibition, and oral anticoagulants.

Measuring quality in atrial fibrillation

Atrial fibrillation is a major health concern as assessed by almost any metric. Over 3 million U.S. citizens have AF, a number that is expected to nearly double by the year 2050. Patients with either paroxysmal or persistent AF have three-to-five-fold increased risk for stroke, and AF accounts for up to 75,000 strokes per year (15% of all U.S. strokes). Furthermore, those with AF have significantly higher mortality and lower quality of life than those without.

Treatment of AF is complex but centers on two major goals: reducing patients' embolic risk and controlling their symptoms. Oral anticoagulant therapies (e.g., VKAs like warfarin) are extremely effective in reducing patients' risk for stroke. However, the use of warfarin is complex and concomitantly can increase patients' risk for bleeding events. Thus, warfarin use is reserved for those with at least moderate stroke risk.

Current American College of Cardiology/American Heart Association (ACC/AHA) AF performance indicators include assessing the thromboembolic risk (CHADS score), initiating warfarin in those with moderate or high risk, and then closely monitoring warfarin therapy to ensure that patients are in a narrow therapeutic range. Opportunities for improvement on each of these performance metrics abound. Depending on the study, only about 30–60% of eligible AF patients in community practice actually receive warfarin therapy. Those at highest risk, as assessed by the CHADS score, are paradoxically less likely to receive warfarin therapy. And even when instituted, time-in-therapeutic range (TTR)—an important indicator of warfarin's safety and effectiveness—ranges from 30 to 60% in community case series. Newer agents, such as the oral direct thrombin and factor Xa inhibitors, represent a major leap forward for antithrombotic therapy for AF. These new drug classes offer easier patient management without constant drug monitoring. Furthermore, relative to warfarin, these new drugs are being demonstrated to have similar or improved thrombotic protection and significantly better safety profiles.

The second goal of AF management is to control patient symptoms and improve quality of life. Rhythm control of AF, either with anti-arrhythmic drugs or with AF ablation procedures, can restore sinus rhythm in many patients with AF. However, studies to date in mildly symptomatic patient subgroups have had difficulty showing that restoration of sinus rhythm necessarily improves quality of life or reduces stroke risks; further research is needed.

New anticoagulants for stroke prevention in atrial fibrillation

Warfarin is effective for stroke prevention in AF but has limitations because of variability in response and an increased risk of bleeding. The most feared complication of warfarin is intracranial bleeding. The efficacy and safety of warfarin is related to the TTR, which is an INR of 2.0–3.0; there is an increased risk of stroke and death at INR < 2 and of bleeding at INR > 3. However, the risk of bleeding, including intracranial bleeding, is present also in patients within the target range. This limits the indication for warfarin to patients with an intermediate-to-high risk of stroke (i.e., with a $CHADS_2$ risk score above 1) to maintain the net clinical benefit.

Therefore, development of new oral anticoagulants aims to demonstrate that they are at least as effective as warfarin and with better safety, allowing use in lower-risk populations. The new alternatives provide more specific inhibition of the coagulation cascade (i.e., by inhibition of thrombin [dabigatran] or factor Xa [apixaban, rivaroxaban, edoxaban, betrixaban]). Currently, the final results from prospective trials comparing these new treatment alternatives to warfarin in patients with AF and an increased risk of stroke are available for dabigatran from the pivotal Randomized Evaluation of Long-term Anticoagulant Therapy Warfarin Compared with Dabigatran (RE-LY) trial performed with a PROBE design. However, prospective double-blind trials comparing apixaban and rivaroxaban, respectively, with warfarin in similar populations have been presented or will be presented within the next year.

The ROCKET AF trial was presented at the AHA Scientific Sessions in November 2010. This study was a prospective, randomized, double-blind, double dummy, parallel-group, multicenter, event-driven non-inferiority study comparing the safety and efficacy of dose-adjusted warfarin with rivaroxaban 20 mg once daily. The primary efficacy end point for non-inferiority in ROCKET AF was the composite of stroke (ischemic and hemorrhagic) and non-central nervous system systemic embolism. The rate of primary outcome per 100 patient-years was 2.12 in the rivaroxaban arm compared with 2.42 in the warfarin arm ($P = 0.117$ for superiority, $P < 0.001$ for non-inferiority). Rivaroxaban also had a slightly better mortality profile: 582 deaths versus 632 in the warfarin group, but the difference was not statistically significant. In a per-protocol analysis, rivaroxaban was superior to warfarin with a primary outcome rate of 1.71 per 100 patient-years versus 2.16 ($P = 0.018$ for superiority and $P < 0.001$ for non-inferiority). Importantly, patients treated with rivaroxaban had fewer intracranial hemorrhages (0.49 vs. 0.74%, $P = 0.019$), fewer critical organ bleeds (0.82 vs. 1.18%, $P = 0.007$) and lower bleeding-related deaths (0.24 vs. 0.48%, $P = 0.003$) than those on warfarin. Rivaroxaban was well tolerated in the study, and rates of discontinuation due to adverse events were similar to those seen for patients on warfarin. One major criticism of the study was the poor INR control compared with previous AF trials. Among warfarin patients, the median time spent within therapeutic range was just 57.8%; they were above therapeutic range 11.9% of the time and below range 19.7% of the time. The results of the study are not published yet.

The RE-LY trial randomized 18,113 patients with AF in 951 sites to blinded fixed doses of dabigatran 110 mg or dabigatran 150 mg twice daily versus unblinded warfarin dose adjusted to INR 2.0–3.0. Median follow-up was 2 years. Rates of the primary outcome were 1.70% per year on warfarin versus 1.55% per year on dabigatran 110 mg (P non-inferiority < 0.001) and 1.11% per year on dabigatran 150 mg (P superiority < 0.001). Rates of major hemorrhage were 3.46% per year on warfarin versus 2.74% per year on dabigatran 110 mg ($P = 0.002$) and 3.22% per year on dabigatran 150 mg ($P = 0.32$). Rates of hemorrhagic stroke were 0.38% per year on warfarin versus 0.12% per year on dabigatran 110 mg ($P < 0.001$) and 0.10% per year on dabigatran 150 mg ($P < 0.001$). Mortality rates were 4.13% per year on warfarin versus 3.74% per year on dabigatran 110 mg ($P < 0.12$) and 3.63% per year on dabigatran 150 mg ($P < 0.047$).

Continued analyses of the RE-LY database have investigated the relative effects of dabigatran in relation to the average time in therapeutic range (cTTR) in each center's warfarin population and to $CHADS_2$ score. The quartiles of cTTR for the warfarin patients were <57, 57–65, 65–73, and >73%. There were no significant interactions with cTTR concerning the superiority of dabigatran 150 mg or the non-inferiority of dabigatran 110 mg versus warfarin for prevention of stroke and systemic embolism and both doses' superiority concerning intracranial bleeding. With dabigatran 150 mg, there was less major bleeding and lower but similar bleeding at higher quartiles of cTTR, while the rates of major bleeding were lower with dabigatran 110 mg irrespective of cTTR. Total mortality was lower with both dabigatran doses at lower cTTR levels and similar at higher cTTR levels.

In the RE-LY trial, around one third of patients had $CHADS_2$ scores 0–1, 2, or 3–6. Increasing $CHADS_2$ scores were associated with increased risks for stroke, bleeding, and mortality, with consistent benefits of dabigatran across all $CHADS_2$ risk groups above 0. Also, patients with the highest risk for new events (i.e., those with previous stroke) had consistent benefits with dabigatran versus warfarin.

Recently, the Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial compared the factor Xa inhibitor, apixaban (5 mg b.i.d.), with aspirin (80–325 mg/day) for stroke prevention in patients with AF who were unsuitable for oral anticoagulation. The trial was prematurely terminated because apixaban was found superior to aspirin in prevention of the primary end point of stroke and systemic embolism: there was a 54% reduction ($P < 0.001$) at a mean follow-up of 1.1 years. There was no significant difference in major bleeding or any other major safety end point. Apixaban was better tolerated than aspirin, with fewer discontinuations of apixaban compared with aspirin (RR 0.88, 95% CI 0.78–1.00, $P = 0.04$).

In summary, for patients with AF, direct thrombin inhibition with dabigatran provides an attractive alternative to warfarin therapy that preserves or improves on the reduction in stroke and systemic embolism achievable with warfarin with similar to lower rates of major hemorrhage. Factor Xa inhibition with apixaban offers a superior alternative to aspirin for stroke prevention in AF patients who are not candidates for warfarin, with even better tolerance than aspirin. The role of rivaroxaban or apixaban in treatment of warfarin-eligible patients awaits peer-reviewed data from ongoing or recently completed studies. Therefore, there is great hope that soon several new treatment alternatives will be available for stroke prevention in AF that should improve both patient outcomes and quality of life.

The relative importance of stroke and bleeding risk in patients with AF: a case-based approach

You are seeing a new patient in clinic. She is an 82-year-old female with hypertension, diastolic heart failure, and non-valvular AF. She has no idea how long she has been in AF, and she reports no change in her symptoms. Her heart rate is irregular, 85 beats per minute, and her blood pressure is 130/80 mmHg. She asks, "Should I start warfarin?" Initially, this seems like a relatively easy question; however, the decision to start a patient on life-long anticoagulation requires a careful assessment of benefits and risks of anticoagulation and consideration of how this information should be used for an individual patient.

Evidence-based medicine, as described by David Sackett, is the process of combining quantitative evidence about medical practice with expert physician judgment to ensure each individual patient the best medical care with reproducible high quality. To provide evidence-based thromboembolism prophylaxis in patients with AF, one has to carefully consider the benefits of thromboembolism prophylaxis (primarily a reduction in the risk of thromboembolic stroke) and the risks of thromboembolism prophylaxis (primarily an increase in the risk of bleeding). These population-based benefits and risks then need to be applied to the individual patient.

The absolute risk of stroke in patients with AF is less related to the burden of AF and more related to patient comorbidities. A number of risk scores have been developed. The most common is the $CHADS_2$ score, which assigns one point for heart failure, hypertension, age $>$ 75 years, and diabetes, and two points for prior stroke. The risk of stroke increases with increasing $CHADS_2$ score, from roughly 2% per year for $CHADS_2$ scores of 0–1 to over 15% per year for $CHADS_2$ scores of over 6. A newer score, the CHADS-VASC, includes points for female sex, vascular disease, and age between 65 and 75 years, and assigns two points for age $>$ 75 years. The CHADS-VASC score better stratifies risk in patients with a $CHADS_2$ score of 0. Our patient has a $CHADS_2$ score of 3 and a CHADS-VASC score of 4. Based on this, her annual risk of stroke is 6–8%. She says, "I'm old and understand I have a risk of stroke, but should I take warfarin?"

There are two additional important factors that have to be incorporated when considering the potential benefits of warfarin for this patient. The first is just how bad a stroke is likely to be and the second is whether warfarin will be effective at reducing the risk of stroke. The definition of stroke used in most of the clinical trials of thromboembolism prophylaxis in patients with AF is non-traumatic, focal neurologic deficit lasting at least 24 h. Thus, some strokes are devastating, while others result in no long-term deficit. However, strokes in patients with AF tend to be severe, with more than two-thirds resulting in death or permanent disability. Also important is that warfarin is highly effective at reducing strokes in patients with AF. Treatment with warfarin results in a roughly two-thirds reduction in stroke. Therefore, our patient has a more than 4% risk per year of a disabling stroke, and her risk of stroke could be reduced to roughly 2% with warfarin.

Warfarin, a potent anticoagulant, has bleeding as its major side effect. Warfarin is most effective in patients who maintain an INR between 2 and 3. With an INR below 2, the risk of stroke promptly increases. With an INR above 3, the risk of bleeding increases. However, even with reasonably good INR control, patients taking warfarin have a roughly 2% annual risk of major bleeding. The risk factors for bleeding substantially overlap with the risk factors for stroke. The recently developed

HAS-BLED score assigns one point each for hypertension, abnormal renal function, abnormal liver function, prior stroke, a history of bleeding, poor INR control, age > 65 years, and drug and alcohol use. The risk of bleeding ranges from 1% with a HAS-BLED score of 0 to more than 15% with a HAS-BLED score of 5. Our patient has a HAS-BLED score of 2 or more; thus, an annual risk of major bleeding on warfarin of 3% or more. She asks, "How bad is major bleeding?"

Like stroke, it is important to consider the range of major bleeding. The definition of major bleeding in most clinical trials of thromboembolism prophylaxis in patients with AF is that of the International Society of Thrombosis and Hemostasis (ISTH). ISTH major bleeding includes fatal bleeding, symptomatic intracranial, intra-articular, intra-spinal, pericardial, intraocular, retroperitoneal, or intramuscular bleeding with compartment syndrome, or bleeding resulting in a fall in hemoglobin of at least 2 g/dl or leading to transfusion of two or more units of red blood cells. In the recently reported RE-LY trial, the rate of major bleeding with warfarin was 3.6%, while the rate of the most devastating intracranial bleeding was only 0.7%. These were in contrast to a stroke rate of 1.6%. Intracranial bleeding is consistently associated with much worse outcomes than other types of major bleeding. When one considers a "net clinical benefit" that includes reduction in stroke and increase in only intracranial bleeding, those patients with a $CHADS_2$ score of 2 or more have a significant benefit with warfarin. This includes our patient above who, with a $CHADS_2$ score of 3, would be expected to have a net benefit of roughly 2% per year with warfarin. Now that we have covered the major efficacy and safety issues with warfarin, our patient asks, "Are there are any other downsides to warfarin?"

Warfarin, although one of the most effective drugs available to prevent devastating consequences of atrial fibrillation, also has significant downsides beyond bleeding. Warfarin has a host of dietary and drug interactions and requires at least monthly INR monitoring; many patients are plagued by significant INR variability requiring frequent dose changes. Finally, and perhaps most importantly, the dietary and drug interactions and the need for frequent monitoring create a constant worry on both the part of the patient and his or her physician. It is for these reasons that warfarin isn't used in close to half of patients with AF, including many of those who are at the highest risk of stroke. Fortunately, for all patients with AF, there are a host of alternatives to warfarin, including factor X and factor II (thrombin) inhibitors that are in development. Some of these may offer better efficacy and/or safety than warfarin, but all are likely to result in less worry; thus, hopefully, we will see more use of effective thromboembolism prophylaxis in patients with AF. Based on this discussion, our patient has decided to start warfarin as thromboembolism prophylaxis, at least until one of these alternative anticoagulants is available.

The anticoagulation of STEMI patients not eligible for reperfusion

In clinical practice, approximately 30% of patients with STEMI will not receive reperfusion therapy, either by primary PCI or lytics, because of delayed presentation, increased risk of bleeding, or patient-related factors. Systemic anticoagulants have been tested in this setting as a way to reduce the occurrence of adverse events, including mortality and re-infarction. A limited number of contemporary trials are available to guide clinical decision-making; however, there is no clear consensus on the use of systemic anticoagulation in this setting.

In a post-hoc analysis of the Thrombolysis in Myocardial Infarction (TIMI) 11B and Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events (ESSENCE) trials, of the 7081 patients initially identified as having non-STEMI, 252 were subsequently found to have Q-wave MI. When treated with enoxaparin instead of UFH, these patients had 28% less death, MI, and recurrent angina at 30 days ($P = 0.04$). These results prompted the Treatment of Enoxaparin and Tirofiban in Acute Myocardial Infarction (TETAMI) trial, which, to this day, remains the only prospective randomized controlled trial specifically testing anticoagulation strategies in STEMI patients not eligible for early reperfusion therapy. TETAMI compared the efficacy and safety of enoxaparin versus UFH and eptifibatide versus placebo in a factorial design. In this context, enoxaparin and UFH were equivalent in terms death, re-infarction, or recurrent angina at 30 days (15.7 vs. 17.3%, respectively; OR = 0.89, 95% CI 0.66–1.21, P = NS). Tirofiban was not superior to placebo to improve outcome and tended to increase the rate of major bleeding.

In a more contemporary setting, the randomized double-blind OASIS-6 trial compared fondaparinux with UFH or placebo in STEMI patients, some of whom who were not eligible to receive reperfusion. In this subgroup, fondaparinux was better than either UFH or placebo at reducing the occurrence of death or MI at 30 days (12.2 vs. 15.1%, $P = 0.04$). Interestingly, the rate of major bleeding among patients treated with fondaparinux was similar to controls (hazards ratio = 0.84, 95% CI 0.47–1.50, $P = 0.55$).

Despite our best efforts, a significant proportion of patients do not receive reperfusion therapy. In 2010, we don't know with certainty that anticoagulation is superior to no anticoagulation in patients with STEMI not eligible for reperfusion.

Antiplatelet therapy in patients undergoing CABG surgery: what should we do?

Antiplatelet therapy significantly reduces mortality in ACS. However, a problem is posed when patients on antiplatelet therapy require cardiac surgery, as this represents a recognized risk for increased surgical blood loss. Formerly, aspirin was suspended for 5 days before surgery; in recent years, this approach has not been routinely followed. In fact, some centers introduce aspirin before surgery, especially when an off-pump technique is employed. The same practice of introducing aspirin before surgery does not occur with clopidogrel, which is most widely used in ACS after drug-eluting stent implantation and before primary PCI for MI. Clopidogrel is administered in emergency rooms when ACS is suspected, even before a definitive diagnosis is made. It permanently blocks platelets, and its effect only diminishes after the natural platelet replacement, which takes 5–7 days in a normal subject. CABG surgery should be avoided during this period, but this is not strictly observed in practice, nor is it clear the magnitude of the contribution of clopidogrel to surgical bleeding. Short-acting and reversible antiplatelet drugs, such as ticagrelor (oral) and cangrelor (intravenous), are being introduced, but they are not yet in general clinical practice. Abciximab, a humanized monoclonal antibody to the platelet GP IIb/IIIa receptor, irreversibly binds the receptor, has a more intensive antiplatelet effect, and should be avoided before surgery. However, the small-molecule GP IIb/IIIa inhibitors (eptifibatide and tirofiban) reversibly bind the receptor, have short half-lives, and have not been shown to increase CABG-related bleeding.

Most guidelines and practicing cardiac surgical centers recommend stopping clopidogrel administration for 5 days before elective surgery. In one multicenter analysis, exposure to clopidogrel within 5 days before CABG was associated with a 9.8-fold increase in need for reoperation ($P < 0.01$). However, other analyses have found weaker or no relationship with reoperation. In urgent situations, the risk of MI or its extension must be balanced against the risk of surgical bleeding, increased morbidity, and possible mortality. Intravenous UFH, on the other hand, could be safely and efficaciously introduced instead of clopidogrel in emergency situations, until a coronary artery anatomical diagnosis is obtained and a decision for PCI or CABG is made. One strategy commonly used is to not administer clopidogrel or prasugrel until the anatomy is known in STEMI patients. However, in NSTE ACS patients, the overall rate of CABG is only 10–15%, and there are no effective methods to predict at presentation who those individuals will be. Thus, the ischemic benefits of early treatment in this situation may outweigh the downsides of delay to CABG if it is ultimately indicated.

In the unstable patient with severe proximal coronary artery lesions, when surgery must be performed in the presence of clopidogrel, some adjuvant measures for better hemostasis may be considered, though few data are available for their effectiveness. These include careful surgical evaluation, the use of prophylactic antithrombotic agents, such as epsilon-aminocaproic acid or tranexamic acid (not aprotinin), during and after the procedure, and platelet infusion.

Statistical issues in the design and analysis of clinical research

As new drugs and devices are developed, questions arise as to the efficacy and safety of these treatments overall and relative to other available treatments, as well as to which patient populations would benefit most from the new therapy. The ideal situation for answering these questions would be to treat the entire population of eligible patients and observe all responses. But it is usually impossible to treat and evaluate every possible patient. Instead, we study the use of the therapy in a sample of the population. Based on the results observed in the sample, we make inferences about what we would expect to see if we could have applied the treatment to the entire population.

Multiple aspects of research determine the level of confidence one can have that the results observed in the sample are real and not just an anomaly of that sample or experiment. The number of patients studied must be large enough to provide adequate power to detect a significant difference. The patients studied should be generalizable to the population of interest. The allocation of treatment to the patients must be in a random fashion to ensure no biases are introduced during the selection process. The blinding of treatment is another important step in eliminating bias. When possible, the treating physician, the patient, and all others involved in the study should be blinded to the treatment that the patient is receiving.

All aspects of the study should be clearly specified and well-defined. When possible, the actual end point of interest should be studied rather than a surrogate end point. For the end point, the definition should be explicitly described, thus allowing for reproducibility in future studies. The protocol should state upfront whether the results will be based on the enrolling physician's determination, independent core laboratory results, or an independent adjudication committee determination of the end point. The timing of the end point should be based on clinical relevance. With long-term outcomes, the short-term results are also known. But the treatment may only affect outcomes acutely, so results may become diluted after an extended period of time.

Randomization of the treatment of interest is not always possible. There are situations in which randomization would be unethical and/or impossible to implement. In these cases, we must instead study series of patients and use special statistical tools to account for biases. These include adjusting for confounders or for the propensity to receive one treatment versus another. If the modeling process can fully adjust for all of the factors that are associated with receiving the treatment and with the outcome of interest, then one can make causal inferences. However, this situation is seldom possible.

With multiple treatments for the same condition, the growing increase of genetic markers, globalization of clinical trials, and many changes in research over the past few years, the analytic issues have become increasingly complex. Statistical expertise is needed to ensure high-quality, accurate results. A greater understanding of the underlying statistical issues in clinical research is needed for the non-statistician, who must critically review and incorporate this ever-growing wealth of clinical information.

Globalization of clinical research

Cardiovascular disease accounts for at least 30% of deaths worldwide (16.6 million people estimated in 2002). Notably, the majority of these individuals are in the low- and middle-income brackets, reaffirming that this is not only a disease of the rich. Projections by Beaglehole and Bonita indicate a growing cardiovascular burden across all income groups such that it is estimated that over three quarters of all deaths will occur secondary to chronic non-communicable disease by the year 2030. Of these non-communicable diseases, cardiovascular disease will be the most dominant. The socioeconomic determinants of this trend provide a compelling impetus to invest in research on health policy and integration of health systems that will enhance the application of available knowledge and close the treatment gaps that exist.

Remarkably, the cost of care bears little relationship to life expectancy: in this regard, the average per capita expenditure across a wide spectrum of countries is $2986 with an average life expectancy of approximately 79 years. At the extremes, Mexico spends slightly more than $800 and the United States in excess of $7000 per capita, yet both have below-average life expectancies indicating the complexity of this relationship. Notably, the Scandinavian countries, Canada, Switzerland, Australia, and France expend more than the median amounts but also have life expectancies in excess of the average.

The Treatment and Outcomes of Acute Coronary Syndromes in India (CREATE) registry offers insight into some of the challenges facing global cardiovascular research. It highlights the relatively young age at which MI occurs, the still dominant incidence of STEMI versus non-STEMI, with mortality from STEMI in excess of 8%. Remarkably, there is a delay from symptom onset to hospitalization of approximately 5 h for STEMI patients and an additional delay from hospitalization to fibrinolysis of nearly 1 h. The large majority of patients are transported to hospital by taxi or private vehicle, but as many as a third use public transportation and only a minority have access to ambulance transportation. As communicated by Prabhakaran, several factors impair research progress in India, including an entrenched bureaucracy, a lack of interdisciplinary and transdisciplinary research, resistance to change across all levels, substantial mobility and instability of the trained workforce, and the dominance of commercial contract research organizations (CROs) with a profit mandate.

On a broader global scale, perverse economic incentives exist in the provision of health care, and there remain huge disparities in access to high-quality health care. Moreover, the chasm between what we know versus how we integrate knowledge, coupled with fear of liability and a sometimes unreasonable quest for diagnostic certainty, contribute to inefficiencies. The treatment-risk paradox is pervasive, and too many dollars are spent on marginal gains or the so-called "flat portion" of the cost–benefit curve.

It is reassuring that there appears to be a renewed understanding of the importance of global academic collaboration based on several factors, including information technology and its transformation of the world into a global village. Moreover, there is a commonality of health-related issues and increasing concern about the costs of health care, which are driving an effort to acquire the best metrics for demonstration of return on investment in health care costs. An increasing number of questions regarding comparative efficacy that require head-to-head evaluations ensures no lack of meaningful projects to undertake. As mortality declines and life expectancy increases in a number of countries, new emphasis on better metrics to assess quality of life has emerged. Striking a balance between the content of care and elements associated with human behavior that contribute to the epidemics of obesity and diabetes remains a major challenge. In this regard, better understanding of the future of personalized medicine and genomics versus broad population approaches is mandatory. An important caveat for research in the developing world relates to statements by both the World Health Organization and the World Medical Organization affirming that, when conducting research in developing countries, it is necessary to ensure that the results of the research will be applicable to those populations in whom it is conducted so that they can benefit from the results.

As one surveys the global treatment gap, it is sobering to contemplate that <10% of global health research is devoted to diseases comprising 90% of the global disease burden. Indeed, a third of the world's population receives only 2% of global health resources, and only 5% of health research is devoted to prevention resources versus 95% dedicated to treatment. Daar et al. highlight six key challenges in tackling chronic non-communicable disease: (1) raising public awareness; (2) enhancing economic, legal, and environmental policies; (3) modifying risk factors; (4) engaging businesses and community; (5) mitigating health impacts of poverty and urbanization; and (6) reorienting health systems.

The VIGOUR Group is well prepared to execute its mission of enhancing worldwide cardiovascular health by the creation, implementation, and evaluation of novel strategies developed through global collaboration. Shared perspectives among group members relate to a strong social conscience and recognition of partnership within a global village. Not only is there an appreciation of the profound unmet needs that exist but also of the mismatch between resources on health expenditures versus key unanswered research questions. In a recent publication by Califf et al. from the VIGOUR Group, four key issues were identified: (1) the lack of definitive evidence to guide care, (2) disease heterogeneity, (3) inadequate funding, and (4) paucity of new leadership. To foster global academic collaboration, infrastructure at all health professional levels is needed, fiscal transparency and stability of academic research organizations (AROs) are required, and the right balance must be struck between individual versus group rewards for achievement. There is a compelling need to develop new leaders and define an appropriate career path for those engaging in these efforts. Each of these issues is associated with opportunities and strategies that will help to drive the cycle of quality on a global basis.

Role of AROs

Conducting high-quality global clinical research is increasingly challenging. The world is "flattening" (Thomas L. Freidman) due to a variety of forces including advances in information technology that allow efficient sharing of data across the globe. However, multiple impediments remain for efficient clinical trial conduct.

Most AROs have three key priorities: (1) patient care, (2) education, and (3) research. These priorities are often reflected in mission statements such as those from the Duke Clinical Research Institute (DCRI), the Brazilian Clinical Research Institute (BCRI), the Canadian VIGOUR Centre (CVC), and the Uppsala Clinical Research Center (UCR). The typical ARO will encompass a variety of research initiatives, including clinical trials, registries, health economics, quality-of-life projects, methodological research, core laboratories, and education. These programs are supported by a framework of coordinating center services. By contrast, missions of commercial CROs are different and typically reflect a goal of maximizing returns or providing efficient services. In a simplistic view, an ARO performs research, and a commercial CRO performs research services.

The United States and many parts of the world are experiencing a shortage of clinical trial investigators and coordinators. Financial pressures and the demands of clinical practice both are central issues of concern, along with growing complexities involving contracts and regulations, lack of training, and less infrastructure to support site-based research at many institutions. Efforts are needed to better understand local site challenges and to respond to those challenges. The Clinical Trials Network, which is part of the National Institutes of Health Roadmap (www.ctnbestpractices.org), provides site investigators with opportunities to learn and network in support of their daily activities.

Cardiovascular disease is and likely will remain the number one cause of death in the world; thus, identifying new and promising therapies is critical. Large clinical outcomes trials will remain the standard for assessing the benefits and safety of new agents, and, as such, clinical trials to evaluate novel therapies will remain large in size and require a global effort. Global clinical research driven by collaboration will be essential to complete these large trials quickly and efficiently. Relationships such as those that have been established between the DCRI and BCRI in Sao Paulo, Brazil, will help create the foundation and infrastructure for performing quality clinical research in the future. Several key priorities for AROs include: (1) creating a culture of excellence and partnership; (2) evaluating novel, efficient, and less costly trial designs and operations; (3) promoting evidence-based medicine and evidence-based trial operations; and (4) developing a sustainable clinical research community through focused support of site investigators. The future has challenges but also exciting opportunities.

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